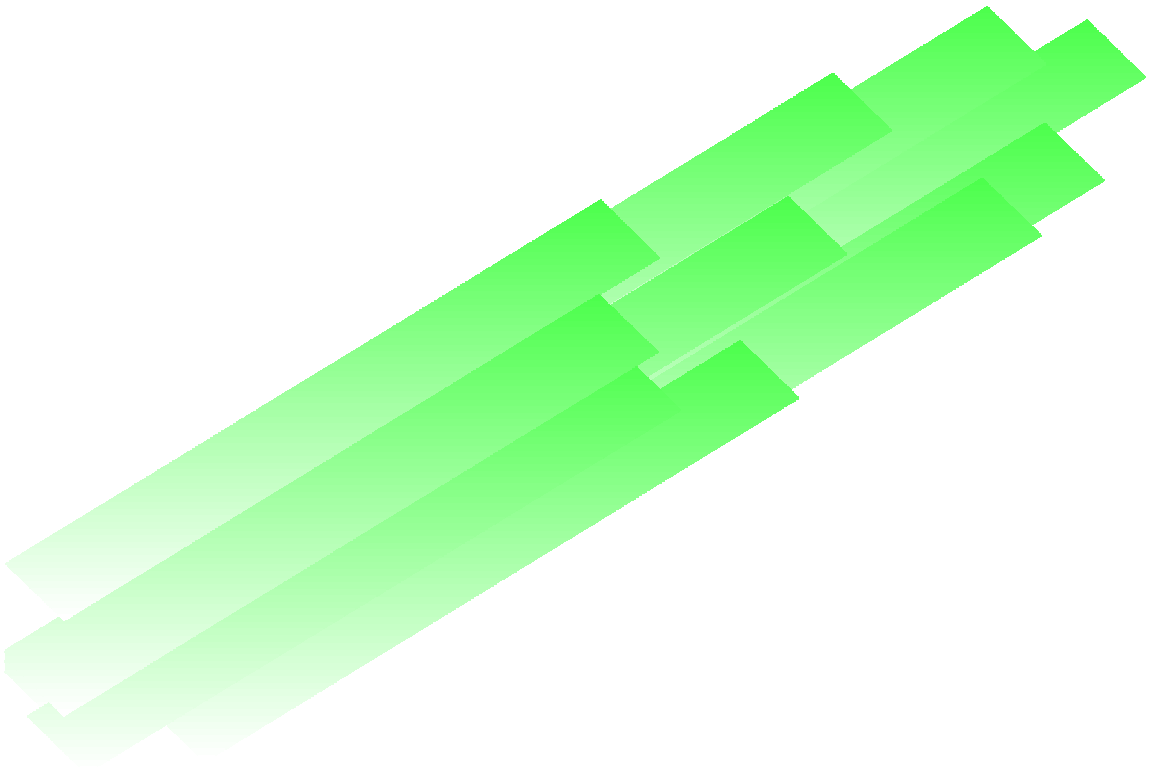
Guidance for Industry

Labeling Guidance for Medroxyprogesterone Acetate Tablets, USP



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (Provera®; Pharmacia and Upjohn Company; 11-839/S-064 and S-067; Approved March 31, 1998). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

A. PHYSICIAN INSERT [See next page.]

[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

MEDROXYPROGESTERONE ACETATE TABLETS, USP

WARNING

THE USE OF MEDROXYPROGESTERONE ACETATE DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED.

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first four months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs, during the first trimester of pregnancy.

If the patient is exposed to medroxyprogesterone acetate tablets during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210° C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. It has a molecular weight of 386.53 and molecular formula $C_{24}H_{34}O_{4.}$ The structural formula is:

[INSERT STRUCTURAL FORMULA HERE]

Each tablet, for oral administration, contains _____ mg of medroxyprogesterone acetate. In addition, each tablet contains the following inactive ingredients: *[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]*

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate, administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered medroxyprogesterone acetate inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

INDICATIONS AND USAGE

Medroxyprogesterone acetate tablets are indicated in secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

CONTRAINDICATIONS

l. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions.
2. Liver dysfunction or disease.
3. Known or suspected malignancy of breast or genital organs.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. As a diagnostic test for pregnancy.
7. Known sensitivity to any component of medroxyprogesterone acetate tablets.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

2. Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their

significance with respect to humans has not been established.

3. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

4. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing neonate and infant has not been determined.

5. Usage in pregnancy is not recommended (See WARNING Box).

6. Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives.[1-4] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products.

PRECAUTIONS

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, non-functional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

5. Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.

6. A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

7. The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

8. The pathologist should be advised of progestin therapy when relevant specimens are submitted.

9. Because of the occasional occurrence of thrombotic disorders, (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations and since the mechanism is obscure, the physician should be alert to the earliest manifestation of these disorders.

10. Studies of the addition of a progestin product to an estrogen replacement regimen for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimen. The potential risks include adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects.

11. Aminoglutethimide administered concomitantly with medroxyprogesterone acetate may significantly depress the bioavailability of medroxyprogesterone acetate.

12. Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term intramuscular administration of medroxyprogesterone acetate has been shown to produce mammary tumors in beagle dogs (see WARNINGS). There was no evidence of a carcinogenic effect, associated with the oral administration of medroxyprogesterone to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

Information for the Patient: See Patient Information at the end of the insert.

ADVERSE REACTIONS

Pregnancy: (See WARNING Box for possible adverse effects on the fetus).

Breast: Breast tenderness or galactorrhea has been reported rarely.

Skin: Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred in an occasional patient. Acne, alopecia and hirsutism have been reported in a few cases.

Thromboembolic Phenomena: Thromboembolic phenomena including thrombophlebitis and pulmonary embolism have been reported.

The following adverse reactions have been observed in women taking progestins including medroxyprogesterone acetate tablets:

breakthrough bleeding
spotting
change in menstrual flow
amenorrhea
edema
change in weight (increase or decrease)
changes in cervical erosion and cervical secretions
cholestatic jaundice
anaphylactoid reactions and anaphylaxis
rash (allergic) with and without pruritus
mental depression
pyrexia
insomnia
nausea
somnolence

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and the following serious adverse reactions: thrombophlebitis; pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

rise in blood pressure in susceptible individuals
premenstrual-like syndrome
changes in libido
changes in appetite

cystitis-like syndrome
headache

fatigue
backache
hirsutism
loss of scalp hair

erythema multiforme
erythema nodosum

nervousness	itching
	dizziness

In view of these observations, patients on progestin therapy should be carefully observed.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

Increased sulfobromophthalein retention and other hepatic function tests.
Coagulation tests: increase in prothrombin factors VII, VIII, IX, and X.
Metyrapone test.
Pregnanediol determination.
Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values.

DOSAGE AND ADMINISTRATION

Secondary Amenorrhea: Medroxyprogesterone acetate tablets may be given in dosages of 5 mg to 10 mg daily for from 5 to 10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of medroxyprogesterone acetate daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing medroxyprogesterone therapy.

Abnormal Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology: Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 mg to 10 mg of medroxyprogesterone acetate may be given daily for from 5 to 10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen 10 mg of medroxyprogesterone acetate daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with medroxyprogesterone. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with medroxyprogesterone.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring, imprints
  Note: All strengths of the innovator's tablets are scored.
- Store at controlled room temperature 15° to 30°C (59° to 86°F).
- Dispense in a tight container, as defined in the USP.

REFERENCES

1. Royal College of General Practitioners: Oral contraception and thromboembolic disease. J Coll Gen Pract **13**:267-279, 1967.
2. Inman WHW, Vessey MP: Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J **2**:193-199, 1968.
3. Vessey MP, Doll R: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J **2**:651-657, 1969.
4. Sartwell PE, Masi AT, Arthes FG, et al: Thromboembolism and oral contraceptives: An epidemiological case-control study. Am J Epidemio1 **90**:365-380, 1969.

The text of the patient insert for progesterone and progesterone-like drugs is set forth below.

PATIENT INFORMATION

Medroxyprogesterone acetate is a progesterone. The information below is that which the U.S. Food and Drug Administration requires be provided for all patients taking progesterones. The information below relates only to the risk to the unborn child associated with use of progesterone during pregnancy. For further information on the use, side effects and other risks associated with this product, ask your doctor.

WARNING FOR WOMEN

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.

If you take medroxyprogesterone acetate and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

- " only" statement.
- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

B. PATIENT INFORMATION INSERT

MEDROXYPROGESTERONE ACETATE TABLETS, USP

PATIENT INFORMATION FOR MEDROXYPROGESTERONE ACETATE TABLETS, USP

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Include name and address of the manufacturer/distributor.
Revision Date.

CONTAINER LABEL

In addition to the general label requirements (“ only” statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name should read as follows:

  Medroxyprogesterone Acetate Tablets, USP

- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.

- We recommend that “ only” appear prominently on the principal display panel.

Side Panel:

- **Note**: Include one Patient Information Leaflet with each prescription.
- Dispense in a tight container, as defined in the USP.
- Store at controlled room temperature 15° to 30°C (59° to 86°F).
- Usual Dosage: See package insert.